59. The method of claim 58, wherein the nucleic acid amplification is reverse transcribed polymerase chain reaction (RT-PCR).

60. The method of claim 57, wherein the binding between the agent and the nucleic acid molecule is determined by a Northern blot assay.

61. The method of claim 38, wherein the disorder is cancer.

Remarks

Claims 1, 6, 7 and 38 have been amended. Claim 1 was amended to clarify the claim language and to excise the non-elected invention of SEQ ID NO:6. Claim 6 also was amended to excise the non-elected invention of SEQ ID NO:6. Support for the amendment to claim 7 can be found in claims 9 and 16 as filed. In view of the addition of its subject matter to claim 7, Claim 16 was canceled. Support for the amendment to claim 38 can be found throughout the specification, particularly in the Examples. New claims were added to specify aspects of the assays used in the diagnostic methods (claims 57-60) and the nature of the disorder diagnosed (claim 61). Support for these claims also can be found in the Examples. No new matter has been added.

Rejection Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected claim 38 under 35 U.S.C. § 112, second paragraph as indefinite. Applicants respectfully traverse the rejection.

The basis of the rejection of claim 38 was asserted to be that "it is not clear what 'characterized' means." Office Action at page 3. Applicants note that the common definition of characterized, i.e., distinguished by, is sufficiently clear to provide one of ordinary skill in the art with a definite indication of what the claimed invention includes. This conclusion is reinforced by the supporting language in the specification that describes disorders characterized by expression of the claimed molecules. In particular, the specification states: "When 'disorder' is used herein, it refers to any pathological condition where the tumor rejection antigen precursor is

expressed. An example of such a disorder is cancer, melanoma in particular." See, specification at page 28, lines 17-19.

The specification also provides an analysis of LAGE-1 expression (see, e.g., Examples 1 and 3, particularly Tables I, II and III). From the results of expression studies, it is clear that one of ordinary skill in the art could readily distinguish a cell or tissue of a disorder as being characterized by the expression of LAGE-1 nucleic acid molecules.

Accordingly, Applicants respectfully request the Examiner to reconsider the rejections of the claims under 35 U.S.C. § 112, second paragraph.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1, 7, 17-19, 38 and 53

The Examiner rejected claims 1, 7, 17-19, 38 and 53 under 35 U.S.C. § 112, first paragraph as lacking an adequate written description. Applicants respectfully traverse the rejection.

The Examiner has alleged that the specification does not provide sufficient descriptive information, such as structural information, to meet the written description requirements set forth in *Regents of the University of California v. Eli Lilly & Co.*

The basic requirement of the written description requirement is that the claimed invention must be described clearly enough to allow one of ordinary skill in the art to recognize that the inventors invented the claimed invention. *Vas-Cath v. Mahurkar* 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991); *Lockwood v. American Airlines, Inc.* 107 F.3d 1565, 41 USPQ2d 1961 (Fed. Cir. 1997); *In re Gosteli* 872 F.2d 1008, 10 USPQ 2d 1614 (Fed. Cir. 1989). The requirement is based on the knowledge of the skilled artisan in the particular art: the applicant must convey to one of ordinary skill in the art through the disclosure in the invention that the applicant was in possession of the claimed invention. The *Lilly* case does not prohibit definition of a genus of nucleic acid molecules by hybridization to a reference sequence. *Regents of the University of California v. Eli Lilly & Co.* 119 F.3d 1559, 43 USPQ 2d 1398 (Fed. Cir. 1997). The *Lilly* case merely states that a DNA molecule must be described by a precise definition, "such as by structure, formula, chemical name or physical properties." *Id.* A genus of nucleic

acid molecules is not routinely defined in the art by a listing of sequences, chemical formulas or chemical names. Instead, the art routinely identifies nucleic acid molecules by hybridization to a particular nucleotide sequence. Hybridization conditions in combination with a reference sequence provide a precise definition of the claimed hybridizing nucleic acid molecules by physical properties. This sort of identification describes the physical properties of a genus of nucleic acid molecules as surely as IR and MS spectra describe the physical properties of a set of chemical compounds.

As one of ordinary skill in the art knows, the claimed molecules must be sufficiently like the reference sequence isolated from melanoma cells to hybridize under a specifically defined set of conditions. Because the person of ordinary skill in the art would recognize, in accordance with the standard practice in the art, that Applicants' invention includes a limited genus of nucleic acid molecules so closely related by physical structure to SEQ ID NO:4 that hybridization under stringent conditions is possible, and further would recognize that Applicants invented the claimed genus based on the description of the genus in the specification, Applicants have fulfilled the requirement of the law for providing an adequate written description of the claimed invention.

One of ordinary skill in the art can readily identify whether a particular sequence is part of the claimed genus by performing a simple and well-established hybridization assay using the hybridization conditions provided in the specification. Thus, because Applicants have provided an adequate written description of the claimed invention, one of ordinary skill in the art will be certain if a particular sequence is, or is not, part of the claimed genus.

SEQ ID NO:4 not only is representative of the claimed genus, but in fact is the sequence to which each member of the genus of nucleic acid molecules is related by physical properties (hydrogen bonding of the complementary hybridizing strands of a double-stranded nucleic acid molecule). Each sequence in the genus, therefore, must be closely related in nucleotide sequence to SEQ ID NO:4 in order to satisfy the definition of the claimed genus.

The Examiner has suggested that the written description rejection could be overcome by amending the claims to recite closed language for the transitional phrase ("consisting of"). Applicants have not amended the claims in this manner because they maintain that the specification supports a broader claim than a claim limited to the specific disclosed sequences. For example, one of ordinary skill in the art would recognize that a nucleic acid molecule having

a single nucleotide difference from SEQ ID NO:4 was within the genus described by Applicants and thus Applicants are entitled to claim such nucleic acid molecules. Similarly, nucleic acid molecules having only a few nucleotide differences from the disclosed sequence are recognizable by one of ordinary skill in the art as belonging to the genus of nucleic acid molecules invented by Applicants. Accordingly, Applicants should be entitled to claim such molecules, having adequately described genus containing such nucleic acid molecules.

Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph based on the statements presented above.

Claim 6

The Examiner also rejected claim 6 under 35 U.S.C. § 112, first paragraph for lack of an adequate written description, because the allelic sequences are not defined. Applicants respectfully traverse the rejection.

Claim 6 depends from claim 1. Accordingly, all of the arguments presented in relation to claim 1 are applicable the rejection of claim 6 as well. As noted above, the claimed genus is adequately described because Applicants have provided the sequence of LAGE-1 (as presently examined, this refers to SEQ ID NO:4) and have provided a description of the conditions under which a member of the genus of nucleic acids are identified. Therefore, Applicants have provided one of ordinary skill in the art with a description against which a potential member of the genus can be compared.

Applicants also have identified the chromosomal location of the LAGE-1 gene. In accordance with the definition of alleles cited by the Examiner, alleles occupy the same chromosomal locus but may differ (slightly) in nucleotide sequence. Because the chromosomal location of LAGE-1 is provided, one of ordinary skill in the art can readily determine if a candidate allele is in fact an allele of LAGE-1 by determining the chromosomal location of the candidate using standard genetic techniques. Applicants also note that alleles are, in most cases, nearly identical to a reference sequences (i.e., SEQ ID NO:4 as now examined), and thus a simple comparison of the sequences of the candidate allele and the reference sequence will generally be sufficient to indicate that the candidate allele is an actual allele. Chromosomal localization would certainly verify a sequence of very substantial identity as an allele.

As part of this particular rejection, the Examiner stated in the paragraph spanning pages 6 and 7 that "the nucleic acid itself is required" for an adequate written description (citing *Fiers v. Revel* [sic, *Fiers v. Sugano*] and *Amgen v. Chugai*). *Fiers v. Sugano* states: "what is required is a **description** of the DNA itself". *Fiers v. Sugano* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (emphasis added). The Fiers court further stated that one could provide an adequate written description of a nucleic acid "such as by structure, formula, chemical name or physical properties". *Id.* Applicants have done just that in the specification, as was described above. Applicants have provided much more than a mere "wish or plan" for obtaining the claimed sequences; Applicants have set forth the physical properties of the genus that includes alleles of SEQ ID NO:4.

In addition, the Examiner states that the genus is "highly variant". Office Action at page 8. This statement does not make sense in the context of a claim for alleles, given that the art recognizes that alleles have substantial identity in nucleotide sequence. Applicants respectfully request reconsideration of this statement and its application as a basis for the written description rejection.

Accordingly, Applicants respectfully request withdrawal of the rejection of claim 6 under 35 U.S.C. § 112, first paragraph.

Claim 38

The Examiner rejected claim 38 under 35 U.S.C. § 112, first paragraph as not enabled by the specification. Applicants respectfully traverse the rejection.

The Examiner focuses on the term "selectively binds" in alleging that there are different degrees of selectivity. Applicants respectfully disagree. Selective binding is a recognized term used in patent claims to indicate that the binding between two binding partners is specific. Applicants used this term because the claim as filed embraced binding interactions of different types, e.g., hybridization between nucleic acids and antibody-antigen binding.

Claim 38 has now been amended in conjunction with the restriction requirement (now made final) to embrace nucleic acid hybridization. In so doing, Applicants reserve the right to pursue additional aspects of the invention of claim 38 as filed in future applications.

One of ordinary skill in the art knows that a variety of hybridization conditions are suitable for use in the claimed methods. This is not a matter requiring anything other than

routine experimentation, as nucleic acid hybridization to a known sequence is well established in molecular biology. Applicants have provided guidance in the form of specific hybridization conditions, as well as working examples pertaining to hybridization and nucleic acid amplification of SEQ ID NO:4.

Applicants must take issue with several of the Examiner's statements concerning this rejection. First, the Examiner stated that "it is well known in the art that under low stringent hybridization conditions, **any compound** would bind to the claimed nucleic acid molecules." Office Action at page 9, emphasis added. Applicants would appreciate receiving a scientific reference that sets forth such a principle. In the alternative, Applicants respectfully request that the statement be retracted. Second, the Examiner stated that it was not clear if there exists a probe specific for SEQ ID NO:4. Office Action at page 9. Applicants respectfully note that Fig. 1 shows a region of SEQ ID NO:4 (clone 2) that is absent from SEQ ID NO:6 (clone 4) and NY-ESO-1 (clone 3). Applicants submit that one of ordinary skill in the art would recognize this region as adequate to distinguish the expression of SEQ ID NO:4 from the other related sequences. With respect to the Examiner's comments about PCR primers, Applicants note that even if primers that bind to all three sequences were used in PCR amplification reaction, the sizes of amplification products are different among the three sequences, and thus are distinguishable by one of ordinary skill in the art.

In view of the amendment to claim 38, Applicants respectfully request that the Examiner withdraw the rejection.

Claim 53

The Examiner rejected claim 53 under 35 U.S.C. § 112, first paragraph as not enabled by the specification. Applicants respectfully traverse the rejection.

The Examiner bases the rejection on an alleged unpredictability of the art. The references used to support this contention were published in 1992 or 1995. Specifically, Ezzell is cited for its review of the "current thinking" (circa 1995) in cancer vaccines in that tumor immunologists had not identified the most effective approach, and in that there was a supposed lack of optimism that a single peptide would trigger an immune response. Regarding the first contention based on Ezzell, the unsettled nature of an effective approach to immunization hardly has a bearing on whether one of ordinary skill in the art would have to exercise undue

experimentation to make and/or use the specific claimed approach (nucleic acid immunization). The scientific literature contains many examples of the use of nucleic acid immunization to generate immune responses. Applicants have included herewith four examples (of many found) of reports of successful nucleic acid-based immunization. As all of the references were published in 1995, it is fair to conclude that one of ordinary skill in the art at the time of filing of this application would not have concluded that the therapeutic success nucleic acid vaccines was unpredictable.

Applicants also note one need not provide information that permits one of ordinary skill in the art "predict the efficacy" (Office Action at page 11) of a therapeutic invention in order to enable that invention. In view of the high level of skill in the art, the routine nature of any experimentation involved, the guidance presented in the specification with respect to the sequence and the expression of the LAGE-1 nucleic acids, Applicants maintain that one of ordinary skill in the art could make and/or use the claimed invention without undue experimentation.

Applicants respectfully request that the Examiner withdraw the enablement rejection of claim 53 in view of the foregoing statements.

Claims 1, 38 and 53

The Examiner rejected claims 1, 38 and 53 under 35 U.S.C. § 112, first paragraph as not enabled by the specification. Applicants respectfully traverse the rejection.

The Examiner has rejected the claims because one of ordinary skill in the art would not be able to predict if SEQ ID NO:4 would be translated into protein. According to the Examiner, one of ordinary skill in the art "would be forced into undue experimentation to practice the claimed invention." Office Action at page 13. In support of these allegations, the Examiner has selected several papers which teach that expression level of a protein does not necessarily correlate with the expression level of its encoding nucleic acid molecule.

Applicants respectfully suggest that the references cited by the Examiner, while scientifically interesting, do not support the legal conclusion that one of ordinary skill in the art would have to engage in undue experimentation to practice the claimed invention. First, the determination of protein expression is routine in the art, and any experimentation accordingly must be viewed as routine. Methods for determining whether a protein are expressed are quite

common and do not require special skill or effort. Second, the references cited indicate that the proteins encoded by the nucleic acids are in fact translated, although not necessarily in proportion to the amount of mRNA produced. In some of the references, protein translation may depend on conditions (iron availability, mRNA secondary structure, etc.). Nevertheless, Applicants assert that one of ordinary skill in the art would not have to engage in undue experimentation to determine if the LAGE-1 protein is translated (even if peculiarities like those cited in the references were to apply; there is no indication that this is so).

The Examiner also suggests that it would require undue experimentation for one of ordinary skill in the art to determine what an immunogenic fragment is. This suggestion is not supported by anything other than the Examiner's statement. Applicants respectfully request that the Examiner provide a literature reference that suggests the difficulties in determining what an immungenic fragment is. Concerning the Examiner's focus on peptides recognized by CTLs, Applicants note that Example 7 provides extensive and detailed guidance on the identification of portions of LAGE-1 recognized by CTLs. Two different methodologies are identified for this purpose, each of which is known to one of ordinary skill in the art. Applicants also suggest the use of computer algorithms for the selection of putative CTL epitopes, and provide appropriate references for such algorithms. The foregoing methods are well known and routine in the art. Moreover, Applicants contend that the determination of immunogenic fragments recognized by antibodies is also routine in the art. Applicants would be happy to supply references to that effect once the Examiner can support the allegation that one of ordinary skill in the art would have to engage in undue experimentation to identify immunogenic fragments of a disclosed protein sequence such as LAGE-1.

The Examiner's recitation of the difficulties of precisely defining an epitope at the molecular level on pages 14–15 of the Office Action misses the mark for supporting an allegation of undue experimentation. The practice of the invention claimed in claim 53 does not require knowledge of the structure of the epitope, as it merely recites an immunogenic fragment of LAGE-1. Thus one of ordinary skill in the art can practice the invention without a detailed understanding of the three-dimensional structure of the epitope.

Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of claims 1, 38 and 53 as not enabled.

Claims 3 and 17-19

The Examiner rejected claims 3 and 17-19 under 35 U.S.C. § 112, first paragraph as not enabled by the specification. Applicants respectfully traverse the rejection.

The basis for the rejection is the alleged unpredictability of the expression of LAGE-1 protein in tumors. This issue was addressed above in the response to the rejection of claims 1, 38 and 53 under 35 U.S.C. § 112, first paragraph, above. As noted above, basing an argument of unpredictability on the selection of unusual cases from the literature of non-correlated protein expression hardly qualifies as valid support for the argument. In the instant case, the claimed LAGE-1 nucleic acid molecule was known to be expressed in tumors. In the overwhelming majority of cases, nucleic acids that are expressed are also translated into protein. The correlation of nucleic acid and protein expression levels relied on by the Examiner to support unpredictability is irrelevant to the claimed invention. Furthermore, as noted above, one of ordinary skill in the art can readily determine the expression of LAGE-1 protein in tumors using standard methods. Thus, the claimed invention cannot reasonably be said to require undue experimentation in its practice, because even if the production of LAGE-1 protein in tumors is unpredictable (which Applicants dispute), such protein production can be determined easily by one of ordinary skill in the art using routine experimentation employing art-standard techniques.

Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of claims 3 and 17-19 as not enabled.

Claims 1, 7, 16-19, 38 and 53

The Examiner rejected claims 1, 7, 16-19, 38 and 53 under 35 U.S.C. § 112, first paragraph as not enabled by the specification. Applicants respectfully traverse the rejection.

To support this rejection, the Examiner stated: "Clearly, it would be expected that a substantial number of the hybridizing molecules encompassed by the claims **would not** share either structural or functional properties with polynucleotides [sic]." Office Action at page 18, emphasis in original.

This reasoning fails to support the rejection for two reasons. First, the Examiner does not provide any reasons why a "substantial number" of molecules encompassed by the claims would be expected not to share these properties. Second, and more importantly, the claimed invention requires that the claimed nucleic acid molecule shares structural properties (sequence

hybridization) and functional properties with SEQ ID NO:4. Therefore, the Examiner's contention that a "substantial number" of molecules encompassed by the claims would not share these properties is in error. Given the disclosure in the specification, the level of skill in the art, and the amount of experimentation required to identify such molecules as meeting the claim requirements (routine experimentation for this art), Applicants assert that one of ordinary skill in the art would not be required to engage in undue experimentation to practice the claimed invention.

Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of claims 1, 7, 16-19, 38 and 53 as not enabled.

Claims 1 and 6

The Examiner rejected claims 1 and 6 under 35 U.S.C. § 112, first paragraph as not enabled by the specification. Applicants respectfully traverse the rejection.

To support this rejection of claims reciting nucleic acid molecules, the Examiner sets forth some of the unpredictabilities of protein chemistry. Applicants do not understand the applicability of the alleged unpredictability of protein chemistry to a nucleic acid invention. Applicants believe that this is an irrelevant and insufficient basis for making an enablement rejection.

Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of claims 1 and 6 as not enabled.

Claim 7

The Examiner rejected claim 7 under 35 U.S.C. § 112, first paragraph as not enabled by the specification. Applicants respectfully traverse the rejection.

The Examiner states that the largest possible unique fragment is one that contains the 247 nucleotide fragment of SEQ ID NO:4 that is not found in SEQ ID NO:8. This construction would ignore all of the fragments of SEQ ID NO:4 that contain all or part of that 247 nucleotide sequence plus other contiguous portions of SEQ ID NO:4. Such fragments also would be unique fragments, and could indeed be as long as 992 nucleotides in length.

To clarify the language of the claims, Applicants have amended claim 7 to recite that the unique fragments include at least 5 contiguous nucleotides of SEQ ID NO:4 that are not present

in SEQ ID NO:8. Because Applicants have provided the sequences of SEQ ID NO:4 and SEQ ID NO:8, one of ordinary skill in the art would not be required to conduct any non-routine experimentation to determine which fragments of SEQ ID NO:4 are unique as circumscribed by the claim.

Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of claim 7 as not enabled.

Claim 38

The Examiner rejected claim 38 under 35 U.S.C. § 112, first paragraph as not enabled by the specification. Applicants respectfully traverse the rejection.

The Examiner states that no disclosure concerning the "overexpression" of SEQ ID NO:4 other than in cancer is found in the specification. Further, the Examiner states that the role of SEQ ID NO:4 in different diseases is not known. Accordingly, the Examiner concludes that one of ordinary skill in the art is not enabled to practice the claimed invention for any disorder except cancer. Applicants respectfully disagree.

The law does not require Applicants to provide a recitation of each and every disorder in which LAGE-1 is overexpressed to enable the claimed diagnostic methods. Future work by others may identify diseases other than cancer that have LAGE-1 overexpression. Nor is the "role" of SEQ ID NO:4 in other diseases required to be known in order to practice a diagnostic method based on detection of expression. Applicants should be entitled to a claim which covers those applications, because it would not require undue experimentation for the skilled artisan to practice the method on such a disorder.

The claimed invention is not a method for the identification of disorders that have LAGE-1 overexpression, which the Examiner appears to suggest in this rejection. The claimed invention merely recites the use of LAGE-1 nucleic acid molecules in the diagnosis of disorders. This invention stems from the identification by Applicants of the expression pattern of LAGE-1. In view of this expression pattern, one of ordinary skill in the art is enabled to diagnose disorders based on the expression of LAGE-1. No undue experimentation would be required, given the level of skill in the art, the disclosure of the specification including working examples, and the minimal quantity of experimentation required.

Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of claim 38 as not enabled.

Rejection Under 35 U.S.C. § 102

The Examiner rejected claims 1 and 7 under 35 U.S.C. § 102(b) as anticipated by the sequence of Zhang et al. (GenBank accession number L39790).

Applicants have amended claim 7 to obviate the rejection. Claim 7 now requires a fragment have at least 15 nucleotides of SEQ ID NO:4.

The rejection as to claim 1 is traversed. The recited prior art sequence encodes a *Mus musculus* fibrillin 2 protein. Claim 1 requires that the nucleic acid molecule encode a LAGE-1 tumor associated polypeptide. The Zhang et al. fibrillin 2 sequence clearly does not meet this claim requirement.

Moreover, the sequence match of the fibrillin 2 fragment with the LAGE-1 molecule is at the 5' end of the LAGE-1 molecule (nucleotides 1-14). This portion of the LAGE-1 molecule is not part of the coding region (which begins at nucleotide 65, see SEQ ID NO:4 in the sequence listing), and therefore the cited fibrillin 2 fragment cannot possible encode a LAGE-1 tumor associated polypeptide as is required by claim 1.

Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of claims 1 and 7 as anticipated by Zhang et al.

Applicants respectfully request reconsideration of the claims in view of the amendments and reasoned statements made above. If the Examiner wishes to advance the prosecution, or if the amendment is unclear, then the Examiner is invited to telephone the undersigned at the telephone number listed below.

Respectfully submitted,

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Amended Claims

1.(amended) An isolated nucleic acid molecule selected from the group consisting of

(a) a nucleic acid molecule which hybridizes under stringent conditions to a molecule having a nucleotide sequence [selected from the group consisting of the nucleotide sequence of] set forth as SEQ ID NO:4 [and the nucleotide sequence of SEQ ID NO:6], wherein the isolated nucleic acid molecule codes for a LAGE-1 tumor associated polypeptide,

(b) nucleic acid molecules that differ from the nucleic acid molecules of (a) in codon sequence due to the degeneracy of the genetic code, and

(c) complete complements of (a) and (b), wherein the isolated nucleic acid molecule excludes nucleic acid molecules having the nucleotide sequence of SEQ ID NO:8.

6.(amended) The isolated nucleic acid molecule of any of claims 1[,] or 2 [or 4], wherein the isolated nucleic acid molecule comprises an allelic variant of a LAGE-1 nucleic acid molecule.

7.(amended) An isolated nucleic acid molecule selected from the group consisting of:

(a) a unique fragment of nucleotides 1-993 of SEQ ID NO:4 between [12] 15 and 992 nucleotides in length, and

(b) [a unique fragment of nucleotides 1-746 of SEQ ID NO:6 between 12 and 745 nucleotides in length,

(c)] complements of "(a)", [and

(d) complements of "(b)",] wherein the unique fragment excludes nucleic acid molecules which consist only of fragments of SEQ ID NO:8, and wherein the unique fragment comprises at least 5 contiguous nucleotides of SEQ ID NO:4 that are not present in SEQ ID NO:8.

38.(amended) A method for diagnosing a disorder characterized by expression of a LAGE-1 nucleic acid molecule or an expression product thereof, comprising:

contacting a biological sample isolated from a subject with an agent that selectively binds the isolated nucleic acid molecule of claim 1 [or an expression product thereof], and

determining [the interaction between the agent and] expression of the nucleic acid molecule [or the expression product] in the sample, wherein the expression of the nucleic acid molecule is diagnostic for [as a determination of] the disorder in the subject.